UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/657,472	09/07/2000	Eric S. Lander	2825.1027-0001	1705

21005 7590 04/21/2003

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/657,472	LANDER ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-44 and 73-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-44,73,75,77 and 79* is/are rejected.

7)☒ Claim(s) *74,76,78 and 80* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/2003;* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☒ Other: *IDS 2/2003* .

DETAILED ACTION

1. Currently, claims 31-44 and newly added claims 73-80 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. This action is FINAL.

2. The rejection under 35 USC 112/first paragraph rejection is maintained with regard to claims 31-44 and newly applied to claims 73, 75, 77, and 79. Response to Applicant's arguments follow.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

4. Claims 74, 76, 78, and 80 are objected to because of the following informalities: the claims are dependent on rejected claims. Applicant's amendment necessitated this new ground of objection. Appropriate correction is required.

New Grounds of Rejection

Enablement

5. Claims 31-44 and newly added claims 73, 75, 77, and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for predicting

the likelihood that an individual will have a myocardial infarction, coronary artery disease (CAD), or coronary revascularization by determining the identity of the nucleotide at position 1186 of SEQ ID NO 3 wherein the presence of a C at position 1186 is indicative of an increased likelihood of a myocardial infarction, CAD, or coronary revascularization as compared with an individual having a G at nucleotide 1186 and wherein the presence of a G at nucleotide 1186 is indicative of a decreased likelihood of having a myocardial infarction, CAD, or coronary revascularization as compared with an individual with a C at nucleotide 1186, does not reasonably provide enablement for a method of predicting increased or decreased likelihood of any vascular disease by detecting a C at position 1186 of any thrombospondin 4 gene or SEQ ID NO 3; or myocardial infarction, or coronary artery disease, or coronary revascularization by detecting a C at position 1186 of any thrombospondin 4 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of determining increased or decreased likelihood of any vascular disease, or more specifically atherosclerosis, coronary heart disease, myocardial infarction, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolisms by detecting a C at position 1186 of any thrombospondin 4 gene or SEQ ID NO 3. The claims are also drawn to a method of predicting the likelihood that a human will have myocardial infarction or coronary revascularization by detecting a C at position 1186 of any thrombospondin 4 gene. The specification, however, only teaches of a study that detected the presence of a C at position 1186 of SEQ ID NO 3 in a group of patients with MI (myocardial infarction) or coronary revascularization. The specification teaches a study wherein 148 of 347

patients had the TSP-4 variant (C at position 1186), and teaches that a statistically significant number of patients carried the TSP-4 variant and thus establishes an association between the TSP-4 variant and MI and coronary revascularization. The specification provides no teaching or examples of the presence of the TSP-4 allele leading to a prediction of increased likelihood of atherosclerosis, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism.

With regard to any thrombospondin 4 gene, the specification provides an example of an association between MI, and patients with coronary revascularization, and a C at position 1186 of SEQ ID NO 3. The specification, however, does not teach how the resulting missense mutation in the protein encoded by SEQ ID NO 3 (alanine to proline) is linked to MI, or coronary revascularization, let alone any vascular disease. Such a teaching is critical to enable the broad scope of the invention as TSP-4 genes are present in different species that have less than 100% identity to SEQ ID NO 3. For example, the mouse sequence has 79% identity, the rat sequence has 78% identity, and Xenopus laevis has 44% identity with positions 500-2000 of SEQ ID NO 3 (sequence alignments provided). Without a teaching from the specification or the art as to the significance or role of amino acid 347 of TSP-4, such as how it interacts with other amino acids within TSP-4 or other proteins involved in the same biochemical mechanism as TSP-4 to achieve wild-type activity, and why or how the presence of a proline instead of an alanine at that position results in an association between MI, CAD, or coronary revascularization in patients, one of skill in the art would not be able to establish a predictable correlation between the substitution of a C instead of a G at position 1186 of any TSP-4 gene from any species and an association between MI or coronary revascularization, let alone any vascular disease in any

individual (encompasses an animal). The specification provides no evidence of a mutation at position 1186 of any other thrombospondin 4 gene, such as a splice variant of SEQ ID NO 4 or TSP-4 from another organism. It is unpredictable whether this position correlates in terms of function with any thrombospondin 4 gene, or whether the exact nucleic acid mutation will result in the same amino acid change. To practice the invention as claimed, the skilled artisan would be required to perform trial and error analysis. Because neither the specification nor the art teach how this position functions in the wild type activity of thrombospondin 4 (SEQ ID NO 3) or how the mutation alters function to provide an association between MI or coronary revascularization, the results of such an analysis are unpredictable and therefore, require undue experimentation.

The claims also broadly encompass increased or decreased likelihood for any vascular disease based on the presence of a C at position 1186 of any TSP-4 gene or SEQ ID NO 3. The specification, however, does not enable the full scope of the claims. The specification teaches of study that found an association between a C at position 1186 of SEQ ID NO 3 and MI or coronary revascularization. The specification provides no teaching of the affect of a missense mutation (alanine to proline) at position 347 of SEQ ID NO 4 on the activity of TSP-4 such that the aberrant protein leads to MI, CAD, or coronary revascularization. Without such teaching, the skilled artisan would be unable to determine how or if the affect of the TSP-4 variant on TSP-4 activity would predictable result in an individual suffering from any vascular disease. Further, the term vascular disease encompasses a large number of disorders that are not all related in terms of biochemical pathways or cause. That is, while a mutation in a gene may be associated with one disease, the mutation may affect the activity in a pathway that is unrelated to other vascular diseases. For example, the On-line Medical Dictionary (cancerweb.ncl.ac.uk/omd/)

defines a peripheral vascular disease as a term used to describe progressive occlusive disease of the arteries that supply the extremities and further teaches that risk factors include diabetes; thromboembolism as an obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel; and a pulmonary embolism as the lodgment of a blood clot in the lumen of a pulmonary artery, causing a severe dysfunction in respiratory function. Neither the art nor the specification provide any teaching of how the TSP-4 variant affects TSP-4 activity to lead to MI, CAD, or coronary revascularization and therefore, it is unpredictable as to whether the affect of the TSP-4 variant will also cause peripheral vascular diseases, thromboembolisms or pulmonary embolisms. To practice the invention as broadly as it is claimed, the skilled artisan would have to perform a large study of patients including patients suffering from a substantial number of different vascular diseases and a control population to determine whether the TSP-4 variant taught in the specification is significantly associated with any vascular disease, or more specifically, atherosclerosis, coronary heart disease, thromboembolisms, etc. As the results of such a study are unpredictable due to the lack of guidance from the specification and the art, such experimentation is considered undue.

Response to Arguments

Arguments with regard to the Lange et al reference were found persuasive. Accordingly, reference to such has been withdrawn in the rejection set forth above. Further, the indication of the scope of enabled subject matter in the rejection set forth above has been changed to include coronary artery disease, in light statistically significant association between the TSP-4 mutation

and CAD taught at page 49 of the specification (lines 19-20). The remaining issues in applicants' response are addressed below.

The response traverses the rejection. The response asserts that applicants have amended the claims to recite methods of "determining likelihood" of vascular disease in a "human" and thereby obviate the portions of the rejection set forth at page 4, through page 6, line 16. This argument and the amendment have been thoroughly reviewed but were not found persuasive to over come the rejection. Firstly, it is noted that claims 41-44 are still drawn to any individual, which includes any species. As stated in the previous office action, the specification does not teach how the resulting missense mutation in the protein encoded by SEQ ID NO 3 (alanine to proline) is linked to MI, or coronary revascularization, let alone any vascular disease. Such a teaching is critical to enable the broad scope of the invention as TSP-4 genes are present in different species that have less than 100% identity to SEQ ID NO 3. For example, the mouse sequence has 79% identity, the rat sequence has 78% identity. Without a teaching from the specification or the art as to the significance or role of amino acid 347 of TSP-4, such as how it interacts with other amino acids within TSP-4 or other proteins involved in the same biochemical mechanism as TSP-4 to achieve wild-type activity, and why or how the presence of a proline instead of an alanine at that position results in an association between MI, CAD, or coronary revascularization in patients. Without such a teaching, one of skill in the art would not be able to establish a predictable correlation between the substitution of a C instead of a G at position 1186 of any TSP-4 gene from any species and an association between MI or coronary revascularization, let alone any vascular disease in any individual (encompasses an animal). Secondly, it is noted that the claims 31, 36, 41, 73, 75, 77, and 79 continue to recite 'position

1186 of the thrombospondin 4 gene", whereas the previous office action indicated "the specification provides no evidence of a mutation at position 1186 of any other thrombospondin 4 gene, such as splice variants of SEQ ID NO 4.... It is unpredictable whether this position correlates in terms of function with any thrombospondin 4 gene." The recitation of position 1186 is an arbitrary designation unless a reference point is given. The response does not address this aspect of the rejection.

With regard to the previous office action's indication that the term 'vascular disease' encompasses a large number of disorders that are not necessarily related in terms of biochemical pathway or cause, the response asserts that the specification teaches a study which determined pivotal genes associated with premature coronary artery disease. The response asserts that a mutation in TSP-1 and TSP-4 emerged as important SNP's associated with these diseases. The response summarizes the teachings of the specification at page 32, with regard to thrombospondins in general. The response concludes that although the study as described in the specification included only two disease groups, the broad reaching effects of TSPs as is described [by the specification] make it reasonable to ascertain that TSPs play a role in the other disease states associated with vascular diseases such as atherosclerosis, coronary heart disease, myocardial infarction, stroke, peripheral vascular diseases, venous thromboembolism and pulmonary embolism. This argument has been thoroughly reviewed but was found unpersuasive. Firstly, while the single mutation in TSP-4 was found to be significantly associated with MI and premature coronary artery disease, the association between the mutation found in TSP-1 which results in an asparagine to serine mutation at position 700 of TSP-1 was less strong (see p. 49 lines 18-25). Further, the specification provides no guidance as to any correlation in the effect

that such mutations would have on the activity of either TSP-4 or TSP-1. For example, it is unclear if these mutations affect the activity of TSP-4 or TSP-1 in the same way. With regard to the teachings in the specification at page 32, the specification teaches that thrombospondins are a family of extracellular glycoproteins that modulate cell behaviors including adhesion, migration and proliferation, that platelets secrete TSPs when activated in the blood by agonists such as thrombin and that TSP's bind to fibronectin and fibrinogen. However, the specification does not teach how such activities relate to any of the vascular diseases claimed, or how the mutation in TSP-4 or TSP-1 affect such activity such that an individual would be at risk for developing any of the claimed vascular diseases. The response asserts "current research indicates a link between platelet-thrombosis and development of atherosclerosis " and cites page 32 of the specification. A thorough review of the specification, however, did not provide any guidance as to how TSP's provide a link between platelet-thrombosis and atherosclerosis. Further, the Crawford et al reference (Cell, vol. 93: 1159; 1998) cited by the specification with regard to this assertion teaches that "TSP-1 is an important natural activator of TGF-B1 in the lung and in the pancreas" (p. 1166 col. 2, "discussion"), and "The identification of TSP-1 as a particularly effective activator of TGFB-1 in the lung and the pancreas and the ability of small peptides to modify its effects in vivo suggest new routes that might be considered to interfere with the progression of such diseases [pulmonary diseases including asthma and cystic fibrosis]". Crawford et al, however do not teach how such activity of TSP-1 is correlated to any of the vascular diseases claimed. The response further asserts that the role of TSP's in vascular events and their role in MI and revascularization provide a reasonable correlation with other vascular disease states. This argument was thoroughly reviewed but was found unpersuasive. The specification does not

teach the role of TSP's in MI or revascularization. Further, the specification does not teach how the role of TSPs in vascular events is associated with MI or coronary artery disease or any of the other vascular diseases claimed. Additionally, the specification does not teach how the mutations in TSP-1 or TSP-4 affect the activity of TSPs such that myocardial infarction or coronary artery disease result. Without clinical evidence that the TSP mutations taught in the specification are also associated with peripheral vascular diseases or pulmonary embolisms, for example, the skilled artisan would have to determine how the mutations taught in the specification affect the activity of TSPs thereby leading to MI or revascularization. Once such an association is made, the skilled artisan would then need to determine if such change in activity of TSP's would affect the vascular system in such a way that any of the vascular diseases claimed would result. Such experimentation represents a large amount of empirical research that still needs to be undertaken to in fact establish a correlation between the TSP mutations taught in the specification and the vascular diseases claimed. As the specification is silent as to such, the skilled artisan would be unable to predict that because the TSP-4 mutation is associated with myocardial infarction and coronary artery disease, it would also be associated with any vascular disease such as pulmonary embolisms, or peripheral vascular diseases.

Conclusion

6. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Newly added claims 74, 76, 78, and 80 are free of the prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
4/10/03